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Antibody responses to inactivated and/or mRNA SARS-CoV-2 vaccination in patients with inborn errors of immunity

Antibody Responses to COVID-19 Vaccines in Immunodeficiency Patients

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Abstract

Aim: Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) poses significant risks for individuals with inborn errors of immunity (IEI). Limited data exists on the coadministration of diverse SARS-CoV-2 vaccine brands with distinct mechanisms of action in IEI patients.

Material and Methods: Our study, encompassing 37 IEI-diagnosed individuals, aimed to compare antibody responses following the administration of inactivated and mRNA SARS-CoV-2 vaccines, both alone and in combination.

Results: Patients with a median age of 30 years (IQR; 23-40.5) received 2 doses (43.2%), 3 doses (37.8%), or 4 doses (18.9%) of SARS-CoV-2 vaccines. The median evaluation time for anti-SARS-CoV-2 antibodies was 199 days (IQR; 90.5-298), revealing an overall seropositivity rate of 91.1% (n=34). Notably, mRNA-vaccinated patients exhibited significantly higher antibody titers than those vaccinated with inactivated vaccines (p=0.014). A positive correlation emerged between the number of vaccine doses and antibody titers (r=0.4081, p=0.009). Furthermore, correlations were observed between serum IgA, IgM, IgE levels, CD19+B cell count, and anti-SARS-CoV-2 antibody titers.

Discussion: The study affirmed the safety and efficacy of inactivated and mRNA SARS-CoV-2 vaccines, either alone or in combination, among IEI patients. With a high seropositivity rate persisting for approximately one year, the findings support the safe administration of three vaccine doses in IEI patients, ensuring prolonged protection. The study identified no severe adverse events, underscoring the vaccines' overall tolerability in this patient population.

Keywords
COVID-19, Inactivated SARS-CoV-2 Vaccine, mRNA Vaccine, Primary Immune Deficiency, Inborn Errors of Immunity

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This study was approved by the Ethics Committee of Marmara University, Faculty of Medicine (Date: 2022-09-08, No: 833)

Introduction

Coronaviruses, belonging to the RNA virus family, are known to cause mild respiratory tract infections. However, following the identification of a new coronavirus (SARS-CoV-2) in December 2019 in Wuhan, China, which led to severe acute respiratory syndromes, it rapidly spread worldwide, causing a pandemic. In Turkey, the first case was announced by the Ministry of Health in March 2020. According to the data from the Turkish Ministry of Health, 17,042,722 people have been infected with SARS-CoV-2, and the number of individuals with mortality is reported as 101,492 [avaible at: https://covid19.saglık.gov.tr/TR-66935/genel koronavirus-tablosu.html].

Inborn errors of the immunity (IEI), formerly referred to as primary immunodeficiency (PID), manifest with various clinical conditions due to approximately 485 genetic defects. While IEI patients often experience frequent and severe infections, autoimmune diseases and malignancies are also common in this patient group. Mortality is mainly associated with infections and their complications. Infections in IEI patients require more prolonged treatment durations compared to the normal population, and opportunistic infections are frequently observed.

SARS-CoV-2 infection poses a serious concern for individuals with immune system defects, as with all infections in immunocompromised patients. Although some studies report mortality rates in these patients similar to the general population [1, 2], other studies have reported up to a 20-fold increase in hospitalization and death rates [3, 7]. COVID-19 can also have a fatal course in individuals without pre-existing conditions, and certain risk factors have been identified, especially in patients, such as male gender, obesity, hypertension, diabetes mellitus, chronic lung, and heart diseases, indicating a higher severity of COVID-19 infection, increased hospitalization, and higher mortality rates. Additionally, mutations causing defects in the Type-I interferon pathway and autoantibodies against Type-I interferon have been detected in a group of previously healthy individuals before encountering SARS-CoV-2, showing an increased risk of fatal COVID-19 infection [8, 9].

Vaccines have proven efficacy in preventing infections and complications and are widely used for treatment and prevention. However, despite the development and widespread administration of vaccines against SARS-CoV-2, it is not yet clear which individuals are still at risk for infection-related mortality. In addition to vaccines, new drugs used in the treatment and the virus's mutation leading to decreased pathogenicity may provide some relief. However, in individuals with immune system defects, the effectiveness of vaccines may be compromised or insufficient due to impaired vaccine response, necessitating comprehensive studies for a clear interpretation of vaccine efficacy.

Several studies reported the seropositivity rate after two doses of mRNA SARS-CoV-2 vaccine, mostly constituting common variable immunodeficiency (CVID), at varying rates [10-14]. Moreover, data on seropositivity after two or more doses and different vaccine combinations are limited.

During the COVID-19 pandemic in Turkey, both inactivated (Sinovac, Coronavac®, vero cell) and mRNA (BNT162b2, Comirnaty®, Pfizer-Biontech) vaccines have been administered. The first inactivated SARS-CoV-2 vaccine was initiated in February 2021 in two doses, followed by a double-dose mRNA vaccine. Initial vaccination was prioritized for healthcare workers and high-risk groups, including immunodeficiency and elderly individuals. Since efficacy studies of vaccines have been conducted on healthy individuals, studies on the efficacy of SARS-CoV-2 vaccines in patients with impaired primary and secondary immunodeficiency are limited.

This study aims to answer questions regarding i) the antibody response to different SARS-CoV-2 vaccines in IEI patients, ii) the combination of inactivated and mRNA vaccines and long-term antibody response, iii) parameters affecting the SARS-CoV-2 vaccine response, and iv) vaccine-related adverse events.

Material and Methods

The study was conducted at two tertiary centers in Istanbul, and patients diagnosed with inborn errors immunity were included if they met the following criteria: i) aged 18 years and above, ii) received a full dose of either inactivated or mRNA SARS-CoV-2 vaccine, iii) received a combination of both vaccines. Individuals who did not receive an adequate vaccine dose and those who had documented COVID-19 infection during the vaccinated or unvaccinated period were excluded from the study. The diagnosis of IEI was established according to the European Society for Immunodeficiencies criteria [15].

Anti-SARS-CoV-2 S kits (Elecsys, Anti-SARS-CoV-2 S, 2022, Germany, Roche) were used to detect anti-SARS-CoV-2 antibodies. The kits predominantly measured antibodies produced against SARS-CoV-2 IgG, along with SARS-CoV-2 IgM and IgA, and analyses were conducted according to the manufacturer's recommendations. Blood samples were collected at the earliest 28 days after the second dose of the vaccine and at any time for those who received three or more doses. Serum samples from patients were measured after dilution at a 1/10 ratio. Anti-SARS-CoV-2 antibody results were considered seropositive if above 0.8 U/ml.

Demographic information, clinical and laboratory evaluations, IEI classification, genetic mutations, comorbidities (bronchiectasis, malignancy, hypertension, diabetes mellitus, autoimmunity, lymphoproliferation, chronic lung disease), regular receiving treatments (including immunosuppressive therapies), immunoglobulin replacement therapy (IgRT) and its administring route, whether immunosuppressive treatment was received during the vaccination period, the number of vaccine doses, vaccination dates, and vaccine brands were recorded through surveys. Immunological tests evaluated within the last year, including lymphocyte subsets, serum IgG, M, A, and E levels, were recorded. Blood sampling from patients receiving regular intravenous IgG treatment was performed before the IgRT receiving, while for those receiving subcutaneous IgG treatment, blood sampling was done independently of IgRT administration.

Statistical Analyses

Median and interquartile ranges were calculated for continuous variables, and frequency measurements were conducted for categorical values. Mann-Whitney U and Student t-tests were used for continuous and ordinal data, and Chi-square and Fisher Exact tests were employed for nominal data. Correlation tests were evaluated using Spearman correlation tests. IBM SPSS 25 (SPSS Inc, Chicago, IL) and GraphPad Prism 8 (GraphPad Software Inc., San Diego, California, USA) programs were used for statistical analyses, and a p-value of <0.05 was considered statistically significant.

Ethical Approval

The study was approved by the Ethics Committee of the Marmara University, Faculty of Medicine (Date: 2022-09-08, no: 833), and informed consent was obtained from all patients.

Results

A total of 43 patients under follow-up with a diagnosis of IEI were evaluated, and 6 unvaccinated patients were excluded from the study. Statistical assessments were performed on a total of 37 patients. The median age of patients was 30 years (IQR; 23-40.5), and 48.6% were female. Table I summarizes the demographic features of the patients in the study. Seropositivity responses were evaluated in patients who received 2 or more doses of inactivated or mRNA SARS-CoV-2 vaccines or a combination of both vaccines. Of the patients, 43.2% received 2 doses (16 patients), 37.8% (14 patients) received 3 doses, and 18.9% (7 patients) received 4 doses of the vaccine. The assessment of anti-SARS-CoV-2 antibodies in 37 patients was performed at a median of 199 days (IQR; 90.5-298). Seronegativity was detected in 3 patients, with 2 having Bruton's disease (X-linked agammaglobulinemia, BTK mutation), and 1 patient was followed up with a diagnosis of CVID with an unknown underlying genetic mutation. The overall seropositivity rate was determined as 91.1% (n=34). Anti-SARS-CoV-2 antibody titers were significantly lower in individuals who received only inactivated vaccines than those who received mRNA vaccines (p=0.014) (Figure 1). A moderately positive correlation was found between the number of doses and anti-

Table 1. Demographic characteristics, vaccination status, and vaccine responses of patients with IEI

Parameters	Results
No of patients	N:37
Age, years (median, IQR)	30 (23-40.5)
Gender (Female %)	18 (48.6)
Diagnosis of IEI	n (%)
PAD	25 (65)
ID	5 (13.5)
CID	5 (13.5)
Phagocyte defects	2 (5.4)
IgRT	n (%)
Intravenous IgRT	18 (48.6)
Subcutaneous IgRT	10 (27)
Prophylactic antibiotics	9 (24.3)
Vaccination of SARS-CoV-2	n (%)
Only mRNA vaccine (2,3 doses)	12 (32.4)
Only inactivated vaccine (2,3,4 doses)	13 (35.1)
Inactivated + mRNA vaccine	12 (32.4)
Anti-SARS-CoV-2 antibody U/ml, (median (IQR)	352 (42.5- 2500)
Immunoglobulins assessment (median, IQR)	
IgG through (mg/L)	862 (723.5-1181)
IgA (mg/L)	26 (9-129)
IgM (mg/L)	48 (19-118)
IgE (mg/L)	0.2 (0.2-16.6)
Lymphocyte subsets (counts, median, IQR)	
CD3+ T	1604 (1009-2231)
CD4+ T	635 (416-1173)
CD8+ T	683 (425-1019)
CD19+ B	118 (46-266)
CD16+-56+ NK cell	109 (30-266)

NK: natural killer, IQR: interquartile range, PAD: Predominantly antibody deficiency, ID: Immune dysregulation CID:Combined Immunodeficiencies

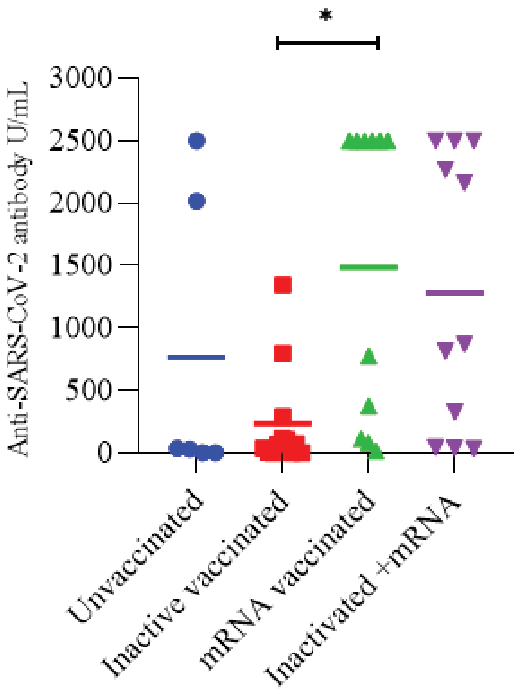

Figure 1. Vaccination status and the titers of anti-SARS- CoV-2 antibodies across different vaccine brands

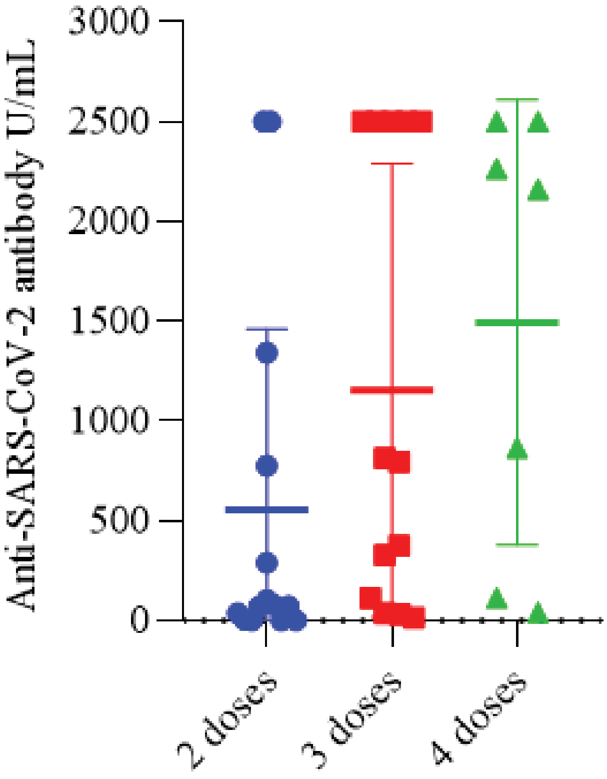

Figure 2. SARS-CoV-2 vaccination doses and the titers of anti-SARS-CoV-2 antibody according to vaccine doses

SARS-CoV-2 antibody titers (Figure 2, r=0.4081, p=0.009).

No significant difference was found when comparing the antibody titers of SARS-CoV-2 vaccinated and COVID-19-recovered individuals with those vaccinated and not encountered COVID-19 (p=0.25). Higher anti-SARS-CoV-2 antibody titers were found in patients not receiving IgRT than those under IgRT (p=0.007) (Figure 3). There were no serious adverse events associated with vaccination. The most common adverse events were redness at the injection site (2 patients), pain, myalgia, fever (1 patient), and maculopapular rash (1 patient after the 3rd dose of mRNA vaccine).

The 6 unvaccinated patients excluded from the study and who were receiving regular IgRT also had blood samples taken to get an idea about anti-SARS-CoV-2 antibody levels in IgG products. Interestingly, even in the unvaccinated group, lower levels of anti-SARS-CoV-2 antibodies were detected compared to the vaccinated group. Simultaneously examined IgG products also showed anti-SARS-CoV-2 antibodies at different titers, up to 2500 U/ml, and seropositivity in the unvaccinated group was thought to be associated with replacement of immunoglobulin G.

In addition, significant positive correlations were found between anti-SARS-CoV-2 antibody titers and serum IgA, M, and E levels (r=0.6677, p<0.001, r=0.5366, p=0.001, r=0.4924, p=0.003, respectively). Also, a significant positive moderate correlation was found between the number of CD19+B cells and antibody titers (p<0.001, r=0.5294).

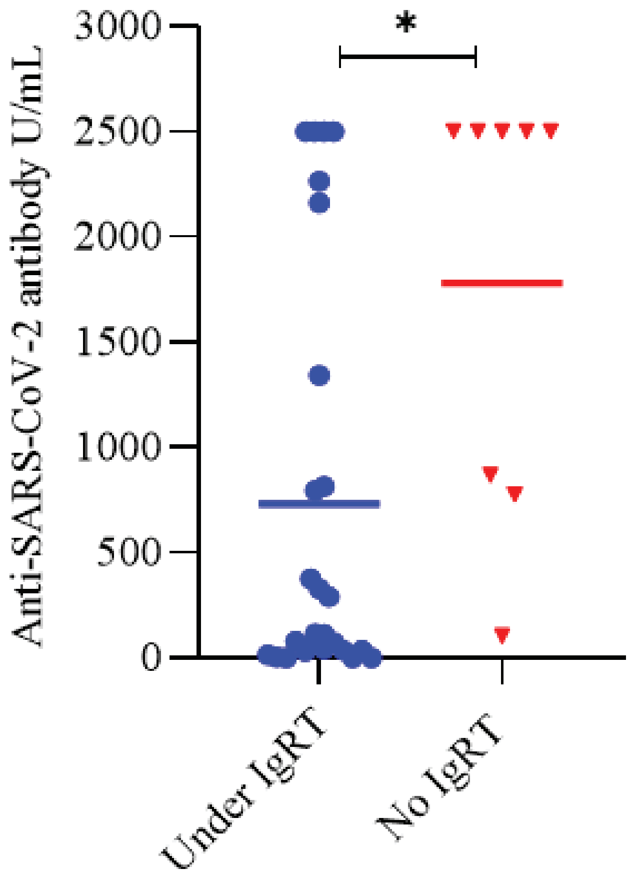

Figure 3. Anti-SARS-CoV-2 antibody titers according to IgRT treatment

Discussion

Evaluating vaccine responses in patients with IEI will provide insights into vaccine effectiveness and reliability in this vulnerable patient group. It is also important for vaccine strategies. In our study, responses to SARS-CoV-2 inactivated and mRNA vaccines were evaluated in 37 patients with IEI, the majority of whom had a predominantly antibody deficiency. Overall seropositivity rate was 91.1%. Two seronegative patients were, as expected, followed up with a diagnosis of Bruton's disease. Patients who received only inactivated SARS-CoV-2 vaccine showed significantly lower anti-SARS-CoV-2 antibody titers than those who received mRNA vaccines (p=0.014) (Figure 1). Also, a moderately positive correlation was found between the number of vaccine doses and anti-SARS-CoV-2 antibody titers. Three or more vaccine doses were well tolerated with a good safety profile, and efficient antibody titers lasting 1 year were detected.

The seropositivity rate after 2 doses of SARS-CoV-2 vaccine in IEI patients varies between 20-83.3% in studies [11, 12, 16-18]. In one study, the antibody response within two months after two doses of mRNA or adenovector SARS-CoV-2 vaccine was found to be 54.8% (n=92/168). This study showed that mRNA vaccines provided more seropositivity and a higher antibody response than adenovector vaccines. Higher IgM levels and CD-19+ B cell counts were found in seropositive patients, and a positive correlation between antibody titers and IgA and M levels was reported [19]. Consistent with the literature, we also found a positive correlation between IgM, A, E, and CD19+B cell counts and SARS-CoV-2 antibody titer in our study, suggesting that these parameters could be used in predicting seropositive vaccine responses.

Another study involving 33 patients with heterogeneous IEI evaluated anti-SARS-CoV-2 IgG antibody levels after two different mRNA vaccines, and seropositivity was detected in only 16 of them. However, in the same study, the antibody response in CVID patients was found to be 80% [13]. Due to the small number of patients in our analysis, antibody responses of different IEI subtypes were not separately evaluated.

The Centers for Disease Control and Prevention (CDC) recommends a third dose of SARS-CoV-2 vaccine in moderate and severe immunodeficiencies. In a study comparing 3 doses of mRNA and inactivated SARS-CoV-2 vaccines in children and adults diagnosed with PID, 16 received mRNA, and 17 received inactivated vaccines [20]. After inadequate antibody response following two doses of vaccine in patients with humoral immunodeficiency, the study suggested that antibody responses increased after the third dose and recommended a third dose for optimal immunogenicity. Seropositivity increased from 55% to 74%. In another study, seropositivity was found to be 76% after the third dose [21]. Our study showed that, regardless of the vaccine brand, as the number of doses increased, anti-SARS-CoV-2 antibody titers also increased, and the high seropositivity rate in our patients might be due to 56.8% of them receiving 3 or more doses. Considering these data, the need for repeated SARS-CoV-2 vaccination in immunodeficiencies should be decided individually by evaluating patients' changing clinical findings and immunological data at intervals.

In another study involving 118 IEI patients investigating the effects of different vaccine brands (adenovirus, mRNA, inactivated, and combined vaccines), seropositivity after two doses was found to be 80.6%. Antibody titers were statistically lower, especially in inactivated and adenovector SARS-CoV-2 vaccinated individuals compared to healthy controls. This study also reported higher antibody titers in mRNA vaccine recipients than in others [22]. Our study also found that antibody titers in patients with inactivated vaccines were significantly lower than those with mRNA vaccines. Interestingly, in individuals receiving combined vaccines (inactivated+mRNA), antibody titers were lower than those with only mRNA vaccines but higher than those with inactivated vaccines. This outcome may be associated with administering a third vaccine dose following two doses of an inactivated vaccine, potentially indicating a booster effect. Additionally, individuals who received a combination of vaccines exhibited lower antibody titers than those who received two doses of the mRNA vaccine; this discrepancy could be attributed to administering a single dose of the mRNA vaccine.

In another study investigating immune responses six months after mRNA vaccination and the effectiveness of the third dose, 425 IEI patients were included. The geometric mean of antibody titers after two doses of mRNA vaccine decreased similarly to healthy controls after an average of 184 days. After an average of 198 days, a third dose of mRNA vaccine was administered to 47 CVID patients, and an increase in antibody titers was observed in 17 patients with low titers after the third dose. No antibody response occurred in the other 30 patients after the second dose, and seropositivity was observed in only 2 patients after the third dose[23]. Our study evaluated antibody titers approximately after six months (median 199 days) of the last vaccination, and seropositivity was still high. In a similar study, anti-SARS-CoV-2 antibody titers and T-cell responses were evaluated approximately 173 days after SARS-CoV-2 vaccination, and in 28 patients (CVID and selective IgA deficiency), seropositivity was still present. T-cell responses also continued in 26 patients, and it was stated that vaccine responses could last up to about a year[24]. However, antibody titers were lower than healthy controls.

In the later stages of the pandemic, it was shown that IgG replacement products contained antibodies against SARS-CoV-2. Therefore, when comparing the antibody levels of those receiving IgRT and those not receiving IgRT, we found that antibody titers were higher in individuals not receiving IgRT. Although this result suggests that the amount of antibodies passed from IgG products is low, it can be considered that the humoral immune systems and antibody responses of immunodeficiency patients who do not need IgRT are functional.

In the literature, three vaccine doses are recommended and shown to increase seropositivity and antibody response. Our study, although with a small number of patients, contributes to the literature regarding patients who have received four doses of the vaccine. It also provides insight into the effectiveness of different inactivated and mRNA vaccine combinations. The combined administration of inactivated and mRNA vaccines in these patients may have provided the development of antibodies not only to the spike protein but also to the N and M proteins. The seropositivity and antibody response did not differ between those who had COVID-19 after vaccination and those who did not. When we compared the antibody titers of individuals who encountered COVID-19 before or after vaccination, we found that having the disease did not affect the titers. Our results were consistent with the literature.

Third and fourth doses of SARS-CoV-2 vaccines in patients with IEI were well tolerated without severe adverse events in our study. Although the number of patients receiving three or more doses was the majority in our analysis, four doses of vaccine did not lead to additional side effects.

Conclusion

Our study showed that inactivated and mRNA SARS-CoV-2 vaccines in IEI patients are safe and effective both alone or in combination. Additionally, a high rate of seropositivity was found in the heterogeneous IEI patient group, and this seropositivity was found to sustain for approximately up to one year. Three doses of the vaccine can be safely administered in IEI patients, and it has been concluded that it is protective for a long time.

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Scientific Responsibility Statement
The authors declare that they are responsible for the article's scientific content including study design, data collection, analysis and interpretation, writing, some of the main line, or all of the preparation and scientific review of the contents and approval of the final version of the article.

Animal and Human Rights Statement
All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or compareable ethical standards.

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Conflict of Interest
The authors declare that there is no conflict of interest.

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